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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
EWOLDT,G	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/347,064	Applicant(s) Eck et al.
	Examiner Gerald Ewoldt	Group Art Unit 1644

☒ Responsive to communication(s) filed on *Feb 28, 2000* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-46* is/are pending in the application.

Of the above, claim(s) *28, 30, 31, and 38-46* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-27, 29, and 32-37* is/are rejected.

☒ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *6*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE

Part of Paper No. 9

DETAILED ACTION

1. Applicant's election without traverse of Group I, claims 1-27, 29, and 32-37, and the species:

A) Effector module:SEQ ID NO:1,

B) Processing module:SEQ ID NO:5,

C) Targeting module:basic fibroblast growth factor (bFGF),

D) Modulating module:SEQ ID NO:3,

E) Affinity module:SEQ ID NO 17,

in Paper No.8, is acknowledged.

Claims 28, 30-31, and 38-46 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

Claims 1-27, 29, and 32-37 are being acted upon. Note that claim 32 is being examined only as it pertains to a nucleic acid.

2. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Applicant should restrict the title to the claimed invention.

3. Claims 8 and 16 are objected to under 37 CFR 1.1821(d) because of the following informalities: the peptide sequences must be identified by SEQ ID NOS.

Appropriate correction is required.

4. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

5. Claims 32-33 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible asserted utility or a well-established utility.

The claims are drawn to a "medicament" for the treatment of a patient with a polynucleotide. The method comprises transporting a polynucleotide across a biological barrier into a cell, wherein the polynucleotide must be translated into protein and the protein then processed and cleaved by the cell. A specific treatment for a specific disease or condition is not defined in the claim nor the specification, however, a general discussion on the use of the medicament for the delivery of a polynucleotide and its potential usefulness for gene therapy is discussed. At the time of the invention was made, successful use of "a medicament comprising a nucleic acid" had not been demonstrated. At the time the invention was made, successful implementation of gene therapy protocols was not routinely obtainable by those skilled in the art. Also absent are any working examples or guidance regarding the method of treatment. While the specification has broadly described a general application for the use of the claimed nucleic acids for gene therapy, essentially all of the work required to ultimately develop therapeutic methods has been left for others.

6. Claims 32-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Enablement is considered in view of the *Wands* factors (MPEP 2164.01 (a)).

Claims 32-33 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible asserted utility or a well-established utility for the reasons set forth above, one skilled in the art would not know how to use the claimed invention so that it would operate as intended without undue experimentation.

Nature of the invention. The claims are drawn to a "medicament" for use in methods of treatment of a patient with a polynucleotide. The method comprises transporting a polynucleotide across a biological barrier to a cell, wherein the polynucleotide must be translated into

protein and the protein then processed and cleaved by the cell.

Breadth of claims. The claims are broad, encompassing delivery of a polynucleotide for treatment of a subject. A specific treatment is not defined in the claim nor the specification, however, a general discussion on the use of the composition for the delivery of a polynucleotide and its potential usefulness for 'gene therapy' is discussed.

State of the prior art. At the time of the invention was made, successful use of "a medicament comprising a nucleic acid" had not been demonstrated. At the time the invention was made, successful implementation of gene therapy protocols was not routinely obtainable by those skilled in the art. Anderson (1998) states that "there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of a human disease" (page 25, column 1) and concludes, "Several major deficiencies still exist including poor delivery system, both viral and no-viral, and poor gene expression after genes are delivered" (page 30).

Working Examples and Guidance in the specification. There are no working examples nor guidance regarding the method of treatment.

Predictability of the art. The physiological art in general is acknowledged to be unpredictable (MPEP 2164.03). Since the applicants have not described all the nucleic acids encompassed by the claims, there is no way to predict efficiency of delivery to nor expression of the polynucleotide in the desired target cell. Further, the specification does not disclose all claimed specific target cells.

Amount of experimentation necessary. Besides the general expectation that it will require years of further research to develop effective gene therapy (Anderson, page 30), it would require extensive research to understand the fundamental biology of the system. Applicants have described a composition for the delivery of a polynucleotide for gene therapy, but essentially all of the work required to ultimately develop therapeutic methods has been left for others.

In view of the of the lack of guidance, working examples, breadth of the claims, skill in the art and state of the art at the time of the claimed invention, it would require undue experimentation by one of skill in the art at the time the invention was made to practice the invention as claimed.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-27, 29, and 34-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nucleic acid encoding a fusion protein consisting of:

A) an effector module consisting of SEQ ID NO:1,

B) a processing module consisting of SEQ ID NO:5,

C) a targeting module consisting of bFGF,

D) a modulating module consisting of SEQ ID NO:3,

E) an affinity module consisting of SEQ ID NO 17,

does not reasonably provide enablement for nucleic acids encoding fusion protein fragments and derivatives thereof, or nucleic acids encoding fusion proteins containing amino acid deletions, substitutions, insertions, additions, or exchanges. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed in claims 1-27, 29, and 32-37 without an undue amount of experimentation. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of protein/peptide compositions broadly encompassed by the claims. The terms "fragment" and "derivative" (claims 1, 16, 34, 36, and 37), and "deletion, "substitution", "insertion", "addition", or "exchange" (claims 2, 3, 4,

and 6) are open-ended and include all homologues, fragments, and synthetic variants of the recited amino acid sequences. The specification fails to provide sufficient guidance regarding the specific properties required to determine whether a polypeptide encoded by the claimed nucleic acid is a functional effector, processing, modulating, targeting, or affinity module. It is known in the art that even **single** amino acid changes or differences in a protein's amino acid sequence can have dramatic effects on the protein's function. For example, the Mikayama et al. reference teaches that the human glycosylation-inhibiting factor (GIF) protein differs from human macrophage migration inhibitory factor (MIF) by a single amino acid residue (see Figure 1 in particular). Yet, Mikayama et al. teaches further that GIF is unable to carry out the function of MIF and MIF does not demonstrate GIF activity (see Abstract in particular). Since the amino acid sequence of a polypeptide determines its structural and functional properties, predictability of which fragments will retain functionality requires a knowledge of, and guidance with regard to, which amino acids in the polypeptide's sequence contribute to its structure and therefore function. The problem of predicting which fragments or derivatives of a protein will retain functionality and which will not is complex and well outside the realm of routine experimentation. Additionally, the specification discloses that efficient intracellular protease cleavage requires the unglycosylated protein as is produced in bacterial vectors, thus claims 25-26 drawn to nucleic acids in glycosylating eukaryotic hosts are not enabled. In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

9. Claims 1-27, 29, and 32-37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

There is insufficient written description to show that, other than a nucleic acid encoding a fusion protein consisting of:

A) an effector module consisting of SEQ ID NO:1,

B) a processing module consisting of SEQ ID NO:5,

C) a targeting module consisting of bFGF,

D) a modulating module consisting of SEQ ID NO:3,

E) an affinity module consisting of SEQ ID NO 17,

Applicant was in possession of a nucleic acid encoding a fusion protein comprising:

A) a "fragment" or "derivative" of the mistletoe lectin A chain (claims 1 and 37).

B) a "fragment" or "derivative" of the mistletoe lectin B chain (claim 16).

C) a "fragment" or "derivative" of the mistletoe lectin propeptide (claims 1 and 36).

The specification defines "fragment" only for the mistletoe A chain and then only as a peptide "which exhibits intracellular toxic activity". The specification fails to define "derivative". The lack of sufficient limitations would therefore allow for *any* number of *any* substitutions, insertions, deletions, exchanges, and/or additions and thus define *any* nucleic acid encoding *any* protein. Further, the specification provides insufficient guidance as to how to identify intracellularly toxic peptides, other than trial and error in a killing assay. One of skill in the art would therefore conclude that the specification fails to disclose a representative number of species to describe the claimed genus. See *Eli Lilly*, 119 F.3d 1559, 43 USPQ2d 1398.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 1, 5, 8, 10-11, 13-16, 26, 34, and 36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

A) In claim 1, 5, 34, and 36, the recitation of the term "degenerate" as it pertains to a nucleic acid molecule, has not been defined in the specification an thus renders the claims ambiguous and indefinite.

B) In claims 10-11, the recitation of the phrase "a cell of the specific immune system" has not been defined in the specification an thus renders the claims ambiguous and indefinite.

C) In claim 13, the recitation of the phrase "a cell of the unspecific immune system" has not been defined in the specification an thus renders the claim ambiguous and indefinite.

D) In claim 14, the recitation of the phrase "a degenerate cell of the immune system" has not been defined in the specification an thus renders the claim ambiguous and indefinite.

E) In claim 8, the symbol "/" and the moiety "S1'" have not been defined and thus render the claim ambiguous and indefinite.

F) In claim 15, the recitation of the abbreviations "strep-Tag", "T7-Tag", "Flag-Tag", and "GFP" render the claim ambiguous and indefinite.

G) In claim 26, the recitation of the abbreviations "*Saccharomyces* sp.", "*Aspergillus* sp.", and "*Spoderoptera* sp." render the claim ambiguous and indefinite.

H) In claim 15, the term "affinity module" has no antecedent basis in base claim 1.

I) In claim 16, the term "modulator module" has no antecedent basis in base claim 1.

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 1-6, 8-14, 16-27, 29, and 34-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over EP 0751221A1 (1997, IDS) in view of Lappi et al. (1994).

EP 0751221A1 teaches:

A) with respect to claims 1-3, 8-14, 16-24, 27, 29, and 36-37 a nucleic acid (DNA and RNA) encoding both the intracellularly cytotoxic mistletoe lectin A (SEQ ID NO:2) (an effector module) and the mistletoe lectin propeptide (SEQ ID NO:6) (a processing module), in addition to a nucleic acid molecule which will hybridize with both. The reference also teaches a vector and an *E. coli* prokaryotic host cell. Further, the reference teaches a proteolytically cleavable fusion protein of the effector and processing modules (see particularly Figure 4c).

B) with respect to claims 1 and 4-6 the reference further teaches a nucleic acid encoding the mistletoe lectin B chain (SEQ ID NO:4) (a modulator module) and a fusion protein comprising effector, processing, and modulating modules (see particularly Figure 4c).

The reference teaching differs from the claimed invention in that it does not teach a fusion protein further comprising a bFGF targeting module.

Lappi et al. teach a fusion protein comprising a plant-derived toxin (effector module) with bFGF for the specific targeting of an immunotoxin to cells expressing bFGF receptors (see particularly page 12552, column 1 paragraphs 2-3).

From the teachings of the references it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to be motivated to combine the bFGF targeting module, as taught by Lappi et al., with the effector-processing or effector-processing-modulating module constructs, as taught by EP 0751221A1, for the specific targeting of the immunotoxin to cells expressing the bFGF receptor, as taught by Lappi et al.

14. Claims 7 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over EP 0751221A1 in view of Lappi et al. as applied to claims 1-6, 8-14, 16-27, 29, and 32-37 above, and further in view of Grisshammer et al. (1995).

EP 0751221A1 and Lappi et al. have been discussed supra. The combined references differ from the claimed invention in that they do not teach the inclusion of a His-tag (SEQ ID NO:17) (an affinity module) in the fusion protein.

Grisshammer et al. teach the use of a His-tag addition to a fusion protein for the facilitation of purification of said protein (see particularly pages 71-73).

From the teachings of the references it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to be motivated to combine the His-tag affinity module, as taught by Grisshammer et al., with the fusion protein, as taught by EP 0751221A1 and Lappi et al., for the efficient purification of the immunotoxin, as taught by Grisshammer et al.

15. No claim is allowed.

16. Foreign patent DE4221836A1, crossed out on the form 1449, filed 10/7/99, has not been considered because an English translation has not been provided.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (703) 308-9805. The examiner can normally be reached Monday through Thursday and alternate Fridays from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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